

Award Number: W81XWH-12-1-0236

TITLE: : EF5 PET of Tumor Hypoxia: A Predictive Imaging Biomarker of Response to Stereotactic Ablative Radiotherapy (SABR) for Early Lung Cancer

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REPORT DATE: September 2016

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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| REPORT DOCUMENTATION PAGE | | Form Approved OMB No. 0704-0188 | |
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| 1. REPORT DATE September 2016 | | 2. REPORT TYPE Annual | |
| 4. TITLE AND SUBTITLE EF5 PET of Tumor Hypoxia: A Predictive Imaging Biomarker of Response to Stereotactic Ablative Radiotherapy (SABR) for Early Lung Cancer | | 3. DATES COVERED 15Aug2015 - 14Aug2016 | |
| | | 5a. CONTRACT NUMBER | |
| | | 5b. GRANT NUMBER W81XWH-12-1-0236 | |
| 6. AUTHOR(S) Billy W. Loo, Jr., M.D., Ph.D E-Mail: BWLoo@Stanford.edu | | 5c. PROGRAM ELEMENT NUMBER | |
| | | 5d. PROJECT NUMBER | |
| | | 5e. TASK NUMBER | |
| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Leland Stanford Junior University 450 Serra Mall Stanford CA 94305-2004 | | 5f. WORK UNIT NUMBER | |
| 9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012 | | 8. PERFORMING ORGANIZATION REPORT NUMBER | |
| | | 10. SPONSOR/MONITOR'S ACRONYM(S) | |
| 12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited | | 11. SPONSOR/MONITOR'S REPORT NUMBER(S) | |
| | | | |
| 13. SUPPLEMENTARY NOTES | | | |

14. ABSTRACT

Purpose and scope:

Stereotactic ablative radiotherapy (SABR) has become a new standard of care for early stage lung cancer in patients who are not candidates for surgery because of excessive surgical risk, and will be an important treatment option for a growing segment of patients with lung cancer. This is particularly true as lung cancer screening efforts are expected to diagnose a greater proportion of lung cancers at earlier stages, yet the aging of the population will lead to a greater proportion of patients having comorbidities that increase surgical risk. Tumor hypoxia is a major known mechanism of radiation resistance and is especially expected to affect very short courses of radiation as in SABR. Imaging using a third generation hypoxia PET agent, ^{18}F -EF5, is a promising approach for noninvasive hypoxia measurement that needs to be validated in the clinical setting.

Our objectives are (1) to understand the prevalence of hypoxia detectable by imaging in early stage NSCLC; (2) to validate ^{18}F -EF5 PET as an indicator of tumor oxygenation status in this patient population; and (3) to evaluate ^{18}F -EF5 PET as a prognostic imaging biomarker for local primary tumor control after SABR.

Progress, results, and major findings:

All institutional and DOD human subjects approvals are complete and current. We have now accrued and completed all study procedures on 15 patients out of the planned total accrual of 43 patients. All scans have been successfully acquired with good technical quality, and follow-up is currently up-to-date for all enrolled patients.

We have conducted a preliminary analysis of the 15 patients with stage I non-small cell lung cancer who received EF5-PET before SABR, and a second pre-SABR EF5-PET scan after either carbogen or DCA administration, and their survival outcomes to date. Six of 15 patients have imageable tumor hypoxia, a rate of 40% (Aim 1). Neither carbogen nor DCA appears to induce a consistent change in EF5 uptake, and the magnitude of the effect if any is such that accruing the full cohort of patients will not provide sufficient power to detect a significant difference (futility criterion met for Aim 2). On the other hand, there is a trend toward worse overall survival in the patients with imageable tumor hypoxia (primary tumor control analysis still pending) indicating that EF5 tumor uptake on PET may be an adverse prognostic factor (Aim 3).

We plan to revise the protocol to eliminate the carbogen and DCA interventions and make the second EF5-PET scan optional, which will greatly increase accrual so that the primary endpoint and the prognostic endpoint will be achieved with the full planned cohort.

Significance:

In summary, our preliminary findings suggest the presence of tumor hypoxia even in relatively small, early stage lung cancer. Additional validation of this finding is pending completion and analysis of our study. Because tumor hypoxia is a strong mechanism of radioresistance, particularly for hypofractionated courses of radiation as in SABR, if validated this finding has substantial implications for the optimal application of SABR to early stage lung cancer. EF5-PET imaging could be useful as a risk stratification factor for clinical trials of lung cancer SABR, and could ultimately be used to individualize therapy for patients with early stage lung cancer.

15. SUBJECT TERMS

Nothing listed

16. SECURITY CLASSIFICATION OF:

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---------------------------------|-------------|--------------|-------------------------------|------------------------|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | USAMRMC |
| U | U | U | UU | 10 | 19b. TELEPHONE NUMBER (include area code) |

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INTRODUCTION:

Stereotactic ablative radiotherapy (SABR) has become a new standard of care for early stage lung cancer in patients who are not candidates for surgery because of excessive surgical risk, and will be an important treatment option for a growing segment of patients with lung cancer. This is particularly true as lung cancer screening efforts are expected to diagnose a greater proportion of lung cancers at earlier stages, yet the aging of the population will lead to a greater proportion of patients having comorbidities that increase surgical risk. Tumor hypoxia is a major known mechanism of radiation resistance and is especially expected to affect very short courses of radiation as in SABR. Imaging using a third generation hypoxia PET agent, ^{18}F -EF5, is a promising approach for noninvasive hypoxia measurement that needs to be validated in the clinical setting. Our objectives are (1) to understand the prevalence of hypoxia detectable by imaging in early stage NSCLC; (2) to validate ^{18}F -EF5 PET as an indicator of tumor oxygenation status in this patient population; and (3) to evaluate ^{18}F -EF5 PET as a prognostic imaging biomarker for local primary tumor control after SABR. If accomplished, these would lay the foundation for future prospective therapeutic clinical trials using ^{18}F -EF5 PET as a stratification factor, and ultimately to individualize therapy.

BODY:

Initiation of this project was initially delayed in response to revisions requested by the DOD human subjects review process. We received the approval memorandum from DOD to start the project on February 13, 2013. The period covered by this report is September 2015 to September 2016, corresponding to months 31-42 of the project timeline in the Statement of Work. The tasks in the Statement of Work and the progress on each are described below.

A. Progress on Statement of Work by task

Task 0. Pre-award preparation (4 months prior to award)

- 0a. Application for Stanford institutional review board (IRB) and scientific review committee (SRC) approval (4 months)
- 0b. Recruitment of clinical research coordinator (2 months prior to award)

Status: Completed during pre-award period.

All institutional and DOD human subjects and SRC approvals are complete and current. A clinical research coordinator is in place.

Task 1. Patient recruitment (months 1-24)

We received the approval memorandum from DOD to start the project on February 13, 2013 (corresponding to Q3). Prior to this we obtained all the required IRB and FDA approvals and recruited a clinical research coordinator (*Task 0*). As such this report covers through Q16, corresponding to through month 42 of the project timeline.

To date, we have accrued a total of 15 patients, compared to the originally planned accrual of 43 patients (which would have completed

accrual for the study) by this time point. Of note, we have screened a total of 88 eligible patients in the same time period, which substantially exceeds the planned number. However, the majority of eligible patients were not enrolled.

The discrepancy between screening and accrual is attributable to multiple factors. Besides the initial wait for study initiation, there were a number of periods of suspended accrual because of (a) downtime of the radiochemistry facility needed to produce the EF5 tracer for PET imaging (Q9-10); (b) a delay in production of the DCA agent from the source compounding pharmacy (Q14-15); (c) turnover of clinical research coordinator staff and temporary internal audit by the Cancer Institute (Q16). However, the most fundamental limitation to accrual has been inability/unwillingness of patients to comply with the logistical demands of completing two serial scans on different days, considering a patient population that often comes from long distances.

Status: Still being completed.

Based on the results of our interim analysis described below, we propose the study design modification described below to eliminate the requirement of one of the scans, which we expect to have a dramatic impact on the ability to accrue patients.

Task 2. Patient follow-up (months 4-34)

Task 2a. Completion of case report forms at each follow-up visit: Follow-ups are complete to date for the enrolled patients. Scheduled follow-up imaging is at 3-month intervals post-SABR. There has been no evidence of local recurrence in any patient at this point, though follow up remains short. To date, two patients have unfortunately passed away.

Status: Complete for enrolled patients.

Task 2b. Review of data from first 5 patients (months 3-5). The study team will assess any technical barriers to collecting all the required imaging data for the first 8 patients, and address deficiencies if necessary: All of the first five patients each successfully completed two EF5 PET scans prior to SABR. Synthesis of ^{18}F -EF5 was consistently reliable with good yield, and there were no technical barriers to scan acquisition or maneuvers to modify oxygenation (carbogen breathing or DCA administration). In addition, there were no technical barriers encountered for any of the subsequent patients to date. This was completed as described in the Y2 annual report.

Status: Complete.

Task 2c. Semi-annual internal data review (every 6 months). The study team will internally audit all data collected on the study to ensure complete collection of study endpoints including imaging data. Missing information will be reconciled: Collection of all imaging and clinical data has been reviewed and is current to date.

Task 3. Data analysis (months 4-36)

Task 3a. Preliminary analysis of ^{18}F -EF5 PET imaging data from first 5 patients (months 3-5). We will evaluate the image quality and technical adequacy to perform all the quantitative analysis specified by the protocol. We will also assess whether modifications to the software are needed to streamline and automate data analysis, and implement the improvements:
We have preliminarily analyzed the EF5-PET imaging data from the first 5 patients. The results were described in the Y2 annual report.

Status: Complete.

Task 3b & 3d. Preliminary analysis of ^{18}F -EF5 PET imaging data from first 20 patients (months 13-15); Scoring of clinical outcomes endpoints in first 20 patients (months 19-24):
We have not yet accrued 20 patients. This analysis will be done when sufficient patients have been accrued, hopefully by the time of the next quarterly report or the subsequent one.

Status: Pending.

Tasks 3c, 3e-g (analyses to be completed when all 43 patients have been accrued)

Status: Pending.

B. Preliminary analysis of data to date

We have conducted a preliminary analysis of the patients accrued so far. Of note, we have been conducting a parallel study of EF5-PET imaging with a very similar design, but for a much broader population of patients with different tumor primary sites, histologies, and stages. Prior to the initiation of the current project, four patients enrolled on our parallel study met the inclusion criteria of the current study and had the same study procedures (ie, early stage NSCLC treated with SABR, with two pre-treatment EF5 scans and tumor oxygenation perturbation intervention as per the current study). As such, our preliminary analysis includes these patients to increase the statistics in this preliminary analysis. Also, we restricted this preliminary analysis to only patients with newly diagnosed primary lung cancer (15 patients), excluding the locally recurrent tumors which will be included in the final analysis.

Figure 1 pertains to aims 1 & 2. Hypoxic fraction here is defined as the proportion of voxels within the tumor that has a higher level of EF5 uptake than the 95th percentile of uptake from the normal reference tissue (aorta/blood pool). Six of 15 patients had imageable hypoxia (defined as hypoxic fraction >10%) at baseline, providing an estimate of 40% of stage I NSCLC tumors having imageable hypoxia (the primary endpoint of the study).

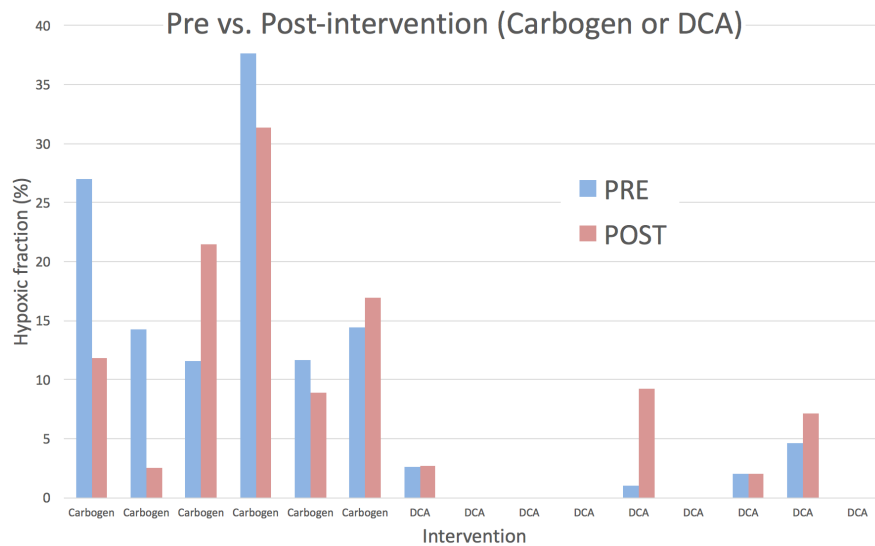


Figure 1

The 6 patients with baseline tumor hypoxia by imaging underwent the intervention of carbogen breathing prior to the second EF5-PET scan. The hypothesized outcome was that this would reduce the hypoxic fraction on the second scan. Conversely, the 9 patients without baseline hypoxia underwent the intervention of DCA administration prior to the second EF5-PET scan. The hypothesized outcome was that this would increase the hypoxic fraction on the second scan.

As shown in Figure 1, neither carbogen nor DCA consistently decreases or increases, respectively, the EF5 uptake in tumors when the initial baseline uptake is high or low, respectively. Based on this preliminary analysis, even if we were to accrue the full cohort of 43 patients, there would be far too little power to find a statistically significant effect of the same magnitude as seen in this initial cohort, *i.e.*, the futility criterion is met for this secondary endpoint of whether these interventions can modulate EF5 uptake (aim 2).

Follow up is ongoing for the secondary endpoint of local primary tumor control (aim 3). Preliminarily, we have evaluated the overall survival of the enrolled patients stratified by the pre-treatment hypoxic fraction determined by EF5-PET imaging (see Figure 2).

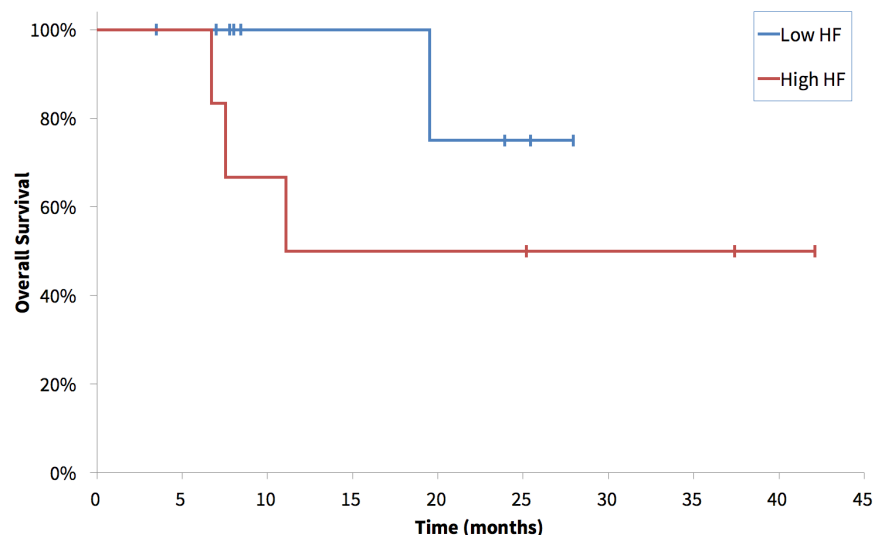


Figure 2

There is a trend toward worse survival when the tumor is hypoxic based on EF5-PET imaging (hypoxic fraction >10%). Completing accrual of the planned cohort will help provide a more robust assessment of whether there is a statistically significant difference, but this preliminarily substantiates the hypothesis that imageable tumor hypoxia is an adverse prognostic factor in early stage lung cancer.

KEY RESEARCH ACCOMPLISHMENTS:

- All human subjects approvals obtained
- Scans of good technical quality
- 88 patients screened, 15 enrolled; follow up current to date
- Preliminary analysis is suggestive of the following:
 - Aim 1: 40% of early stage lung cancers are hypoxic by EF5-PET imaging
 - Aim 2: Neither carbogen nor DCA provide consistent modulation of EF5 uptake
 - Aim 3: Increased tumor uptake of EF5 on PET correlates with worse survival

REPORTABLE OUTCOMES:

None to date.

Publication of results (Task 4 of Statement of Work) will be done upon completion of the accrual and follow up of study patients.

CONCLUSIONS: Summarize the results to include the importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.

The preliminary analysis to date supports the hypothesis that a substantial proportion of patients with early stage non-small cell lung cancer, 40% in this initial cohort, have tumor hypoxia that can be detected by EF5-PET imaging (Aim 1). A more detailed image analysis is ongoing to optimize the quantitation of tumor EF5 uptake. This includes evaluating the stability of uptake in the background regions between the serial scans and whether the background in muscle or the mediastinal blood pool may be a more appropriate reference; evaluating the sensitivity of region of interest delineation to lesion size and partial volume effects and if so, approaches for mitigating these effects.

With respect to the endpoint of being able to detect a change in tumor oxygenation status after interventions, *i.e.*, carbogen and DCA, expected to perturb tumor oxygenation (Aim 2), the preliminary analysis indicates that the statistical futility criterion has been crossed such that even complete accrual of the planned enrollment will not provide adequate power to detect a significant difference of the observed magnitude.

On the other hand, the preliminary overall survival analysis suggests that imageable hypoxia based on EF5-PET may be an adverse prognostic factor (Aim 3). Analysis of primary tumor control is still in progress.

Based on the number of eligible patients screened, we anticipate that our patient volume will be sufficient to complete this study. However, clearly a substantial barrier to patient enrollment is the logistical challenge of coming for two extra appointments to receive the two EF5-PET scans. Particularly because SABR offers a much shorter treatment course than conventional radiation therapy, similar to surgery that involves a short course of treatment, patients are coming for treatment from a large geographic region. Extra trips present a significant burden to these patients.

Action plan: To address this issue, we will modify our protocol to eliminate the carbogen and DCA interventions and make the second EF5-PET scan optional. The primary endpoint of assessing the proportion of patients with imageable hypoxia on pre-treatment EF5-PET would remain unchanged (Aim 1). Similarly, the secondary endpoint of correlating primary tumor control with pre-treatment EF5-PET would also be unchanged (Aim 3). Only the endpoint of evaluating change in EF5-PET before and after the carbogen/DCA intervention (Aim 2) is affected, but the interim analysis finding statistical futility on this endpoint indicates that it is no longer meaningful to complete this portion of the study in any case.

We anticipate that this should greatly increase the ability to accrue patients and meet the intended accrual goal.

In summary, our preliminary findings suggest the presence of tumor hypoxia even in relatively small, early stage lung cancer. Additional validation of this finding is pending completion and analysis of our study. Because tumor hypoxia is a strong mechanism of radioresistance, particularly for hypofractionated courses of radiation as in SABR, if validated this finding has substantial implications for the optimal application of SABR to early stage lung cancer. EF5-PET imaging could be useful as a risk stratification factor for clinical trials of lung cancer SABR, and could ultimately be used to individualize therapy for patients with early stage lung cancer.

REFERENCES:

None to date.

APPENDICES:

None.